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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/471,703	MERENKOVA, IRENA N.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Jehanne Souaya.

2. Currently, claims 69-88 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are newly applied. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 69-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 69-88 are indefinite in the recitation of "nucleotides 5' of a variant nucleotide at the polymorphic site". The claim does not make clear what the 5' is in relation to. For example, if it is in relation to the target sequence, then the claims would be drawn to a method wherein the primer for primer extension actually covers the variant nucleotide. For example, see the diagram as shown in Hoogendorn (p. 89, fig 1). The instant claims recite the "3' end of the

primer is one or more nucleotides 5' of a variant nucleotide at the polymorphic site". With regard to the Hoogendorn figure, on the 5' side of the variant nucleotide would encompass a primer whose 3' end or 3' terminus (it is noted that the recitation of"3' end" is not limited to the 3' terminus, but encompass the 3' region of the primer) are on the 5' side of the variant, which means that the primer would actually cover the variant polynucleotide. However, as indicated by the specification, applicant's method involves primer extension depending on the sequence of the variant nucleotide. This rejection can be easily overcome by reciting instead -- one or more nucleotides 3' of a variant nucleotide, relative to the target sequence orientation, at the polymorphic site--. It is noted that rejections under 35 USC 103 below are drawn to this recitation as the examiner assumes that this interpretation, with regard to the specification's teachings, was applicant's intent.

B) Claims 69-88 are indefinite in the recitation of "one or more nucleotides" as it is unclear if this recitation is meant to encompass sequences immediately adjacent to the polymorphic site. From the response's arguments with regard to the claim amendments, it appears that applicant intends there to be at least a one nucleotide space between the polymorphic site on the target and the 3' terminus of the primer. However, claim 70, which is dependent from claim 69, recites "3' end is immediately upstream of the variant nucleotide" which necessarily stipulates (due to the claim's dependency from claim 69) that the recitation of "one" means immediately adjacent to the polymorphic site.

C) Claim 69-88 are indefinite in the recitation of "3' end" as it is unclear if such refers to the 3' region of the primer or the 3' terminus of the primer.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 69-74, 76, and 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soderlund et al (EP 0648280, published April 19, 1995-herein referred to as Soderlund) in view of Hoogendorn et al (herein referred to as Hoogendorn) and Kuppaswamy et al (hereinafter referred to as Kuppaswamy).

It is noted that the recitation of "one or more" or "at least one" in the claims has been interpreted to encompass primer annealing immediately adjacent to the polymorphic site, except for claim 71, which has been interpreted to encompass a one nucleotide space between the polymorphic site and the hybridization of the 3' terminus of the primer (the primer anneals to the 2nd nucleotide, the site immediately adjacent to the polymorphic site is the first nucleotide). It is further noted that the recitation of "plurality of dNTPs" is interpreted to encompass more than one of the same dNTP.

Soderlund teaches (example 9; Fig. 1d) a method for determining the identity of the polymorphic nucleotide in a target sequence having at least two known variants comprising obtaining a sample containing the target sequence, hybridizing a primer upstream of the variant nucleotide, performing a first extension reaction in the absence of a dNTP complementary to the first known variant but in the presence of a dNTP complementary to the second known variant and a second extension reaction in the absence of a dNTP complementary to the second known

variant but in the presence of a dNTP complementary to the first known variant (pages 4-7). Soderlund teaches that a target DNA fragment containing each of the variant nucleotides is produced by PCR amplification followed by purification of the target sequence from the PCR reaction components by immobilizing the target sequence to a solid support, followed by addition of a primer which hybridizes 3' of the polymorphic site which is annealed to the target. Soderlund teaches that extension occurs in the presence of a labeled dNTP complementary to the mutant nucleotide or to the normal nucleotide. Soderlund teaches analysis of the nucleotide extension by elution of the extension products and analysis of the labeled dNTP with a scintillation counter. Soderlund teaches many different variations to the method, for example, a) Soderlund teaches that the use of dideoxynucleotide triphosphates is not required, and is an optional variation (Fig 1, alternative "d"; p. 7, lines 12-12; example 9 p. 17), b) Soderlund teaches that more than one deoxynucleotide triphosphate can be used and the 3' terminus of the primer can be "n" nucleotides away from the 3' side of the polymorphic site, wherein the only limitation that must be considered is that nucleotide sequences between the 3' end of the primer and the variable nucleotide to be detected must not contain a nucleotide residue of the same type as the one to be detected (see para bridging pages 3-4) (instantly pending claim 71), and c) Soderlund teaches using more than one dNTP in the primer extension reaction (see p. 7, lines 17-20, and also example 2).

The method of Soderlund is different from the claimed method only in that Soderlund teaches that the dNTPs are labeled and that detection of the extension products was performed by detecting the label (ie: if more than one dNTP is present in the reaction, then each is differently

labeled) and does not specifically teach detection of a length difference by HPLC, capillary electrophoresis, or slab gel analysis.

However, Hoogendorn teaches a method similar to that of Soderlund, however the methods differ in that Hoogendorn teaches using an unlabeled dNTP and a ddNTP (to terminate the extension reaction) and the extension products are analyzed not by the presence of a label, but instead by detecting length differences by HPLC. Hoogendorn teaches that the extension product is analyzed to determine length by HPLC, and teaches that the reactions can be multiplexed and that the extension products can be analyzed separately or as pooled samples by HPLC (see p. 90).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Soderlund (use of labeled dNTPs) with unlabeled dNTPs as used by Hoogendorn and to detect the extension on the basis of size differences using chromatography as taught by Hoogendorn. The ordinary artisan would have been motivated to substitute the labeled dNTPs used by Soderlund, with the unlabeled dNTPs of Hoogendorn, in the method of Soderlund, for the purpose of improving the method of Soderlund in that the use of harmful, radioactive labels, would no longer be required for detection of extension reactions. Hoogendorn teaches a desirable alternative detection method that does not require the use of radioactively labeled extension reactions. The ordinary artisan would have had a reasonable expectation of success that the alternative detection method of Hoogendorn would be successful for the detection of extension reactions in the method of Soderlund because Hoogendorn teaches that primer extension and HPLC detection is simple and has the advantage of being easily automated (see abstract). Hoogendorn further teaches advantageous variations,

such as multiplexing, and the ability to identify single base differences up to 70 bases based on use of the column taught by Hoogendorn (see p. 92, col. 2, end of last full para).

Further, given that Soderlund teaches that the use of dideoxynucleotides was optional, the ordinary artisan would have immediately recognized that the use of dideoxynucleotides was not required in the method of Hoogendorn. The use of dideoxynucleotides, as taught by both Soderlund and Hoogendorn, is for the purpose of ending extension at a fixed point, thereby inherently providing for a primer extension product with a fixed, already known length. However, such is not essential for use in the primer extension reactions as Soderlund teaches that the use of dideoxynucleotides in the primer extension reaction is optional and further. Such is evidenced by example 9 of Soderlund as well as the teachings of Kuppaswamy which used primer extension to determine the identity of a polymorphic variant, wherein the primer extension reaction is similar to both the methods taught by Soderlund and Hoogendorn, but that excludes the use of dideoxynucleotides in the primer extension reaction. Further, given that all the references teach that the methods are particularly useful when the identity of a specific variant is required in a particular sample, that is, wherein the sequences of the regions containing the polymorphic variant were known prior to analysis, it would have been obvious to the ordinary artisan that the reaction mixtures containing dNTPs for primer extension would necessarily lack a specific dNTP, and as such, the primer extension reaction would terminate when incorporation of the missing dNTP would be needed, providing for primer extension product lengths that could be anticipated in advance. Given that Hoogendorn teaches that the identity of the incorporated nucleotide is determined by the length of the primer extension product, it would have further been obvious to the ordinary artisan that the detection method of

Hoogendorn could be successfully used in the absence of dideoxynucleotides, because the length of the primer extension product would end at a fixed point, without the use of dideoxynucleotides, and that such point could be anticipated given that the identity of the nucleotides surrounding the polymorphic variant was already known and given the choice of dNTPs used in the primer extension reaction could be manipulated (it is noted that this is how the primer extension reaction in the method of Kuppaswamy is terminated, no dideoxynucleotides are used).

It is noted that Soderlund teaches immobilizing the target to a support and performing primer extension on the immobilized target followed by elution of primer extension product for analysis of label, whereas Hoogendorn teaches primer extension on a target in solution. Hoogendorn then teaches applying the primer extension reaction (includes target and extension product) to an HPLC column for detection of primer extension product based on size. However, the purpose of immobilizing the target as taught by Soderlund was for the purpose of purifying the target from the previous amplification reaction and is not a requirement for the primer extension reaction. To achieve the same result (purification of target DNA from initial PCR reaction) Hoogendorn teaches applying the target to a DNA purification column and Kuppaswamy teaches applying the amplified target to a gel and extracting the purified target. Once purified, the target DNA is available for use in the primer extension reaction. Therefore, it would have further been prima facie obvious to the ordinary artisan that different variations existed for achieving purification of the target for subsequent use in primer extension reactions, and that the step of immobilizing the target to a support, as illustrated by Soderlund, was not the only way to achieve such a result, that is, the target DNA could have been alternatively purified

as taught by Hoogendorn or Kuppaswamy. As such, the ordinary artisan would have recognized that the primer extension reaction of Soderlund, as modified by the teachings of Hoogendorn, for use in the detection method of Hoogendorn could be easily adapted to work together as the ordinary artisan would have immediately recognized that either the eluate containing primer extension products as taught by Soderlund could be applied to the HPLC column of Hoogendorn, or alternatively, the target of Soderlund could be purified either by the method of Hoogendorn or Kuppaswamy, and subsequently used for the primer extension.

Response to Arguments

The response traverses the previous rejection. The arguments in the response will be addressed in so far as they apply to the rejection set forth above.

The response asserts that one advantage of the claimed method is that it allows for detection of both the presence and absence of a variant of interest in a single reaction mixture. This argument has been thoroughly reviewed but was found unpersuasive as such would be the case if the primer were to anneal more than one nucleotide from the polymorphic site. All but claim 71 are drawn to such an embodiment as set forth in the 112/2nd and 103 above. Further, Soderlund teaches a variation of the method of Soderlund wherein the 3'terminus of the primer anneals more than one nucleotide from the 3' side of the polymorphic site. It is further noted that the claims recite the term "comprising" such that the claims are not limited to a single reaction mixture.

7. Claims 75 and 77-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soderlund in view of Hoogendorn and Kuppaswamy as applied to claims 69-74, 76, and 82-83

above, and further in view of Gibson et al (Journal of Capillary Electrophoresis, vol. 5, pp 73-80, Jan-Apr 1998; hereinafter referred to as Gibson).

The teachings of Soderlund in view of Hoogendorn and Kuppaswamy are set forth above. Soderlund in view of Hoogendorn and Kuppaswamy do not teach analyzing the primer extension product using slab electrophoresis or capillary electrophoresis with an intercalating agent that is either ethidium bromide or an unsymmetrical cyanine dye. However, Gibson teaches the separation of DNA by size (in other words, length) using capillary electrophoresis with cyanine intercalation dyes (see abstract). Gibson teaches that with regard to capillary electrophoresis and DNA intercalation dyes, the use of the reaction buffer is important in determining the dye used (see p. 76, col. 1). Gibson teaches that ethidium bromide provides better separation in DNA analysis with TBE buffer. Gibson further teaches that with TAPS buffer, the monomeric cyanine dye PO-PRO-3 provided better separation. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that capillary electrophoresis could be used as an alternative to HPLC to analyze the length of primer extension products according to the method of Soderlund in view of Hoogendorn and Kuppaswamy, as capillary electrophoresis was used for the separation and analysis of DNA fragments according to length. It would have been further prima facie obvious to the ordinary artisan that the capillary electrophoresis method of Gibson could be used because Gibson teaches the successful separation of DNA fragments according to size, using capillary electrophoresis, and further, Gibson teaches ways of improving separation depending on reaction conditions. It would have been further prima facie obvious to the ordinary artisan to use either ethidium bromide or an unsymmetrical cyanine dye depending on the contents of reaction mixture buffer as Gibson

teaches that each have better separation resolution depending on buffer used. The ordinary artisan would have recognized that capillary electrophoresis could be used as an alternative to HPLC, for example under circumstances wherein HPLC equipment was unavailable for primer extension product analysis, and would have been motivated to use the method of Gibson as Gibson teaches the successful separation of DNA fragments according to size, using capillary electrophoresis. With regard to slab electrophoresis, the use of such was well known in the art for separation of DNA according to length and was readily used for such purposes. In addition, slab gel electrophoresis provided a lower cost alterative to the use of capillary electrophoresis and HPLC. Therefore, it would also have been prima facie obvious to the ordinary artisan at the time the invention was made that slab gel electrophoresis could also be used as an alternative to HPLC for detection of primer extension products based on length in the method of Soderlund in view of Hoogendorn and Kuppaswamy. The ordinary artisan would have been motivated to use slab gel electrophoresis as an alternative to HPLC or capillary electrophoresis because such would have provided a less expensive analysis method as compared to capillary electrophoresis or HPLC.

8. Claims 81, 82 and 84-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Soderlund in view of Hoogendorn and Kuppaswamy, as applied to claims 69-74, 76, and 82-83 above, and further in view of Krook et al (Human Molecular Genetics, vol. 1, pp 391-395, 1992; hereinafter referred to as Krook).

The teachings of Soderlund in view of Hoogendorn and Kuppaswamy are set forth above. Soderlund in view of Hoogendorn and Kuppaswamy do not detecting a plurality of target

sequences wherein the different primers for primer extension reaction of the plurality of targets are of different length. However, Krook teaches further alternative variations to the method of primer extension as taught by Soderlund and Hoogendorn and Kuppaswamy. For example, Krook teaches using multiplexed or pooled single nucleotide primer extension reactions using more than one primer for extension wherein the primers are of different lengths (see p. 392, col. 1). The method of Krook is similar to the primer extension methods of Soderlund and Hoogendorn and Kuppaswamy except that Krook specifically teaches multiplexing examples wherein a plurality of primers are used to detect different polymorphic sites in more than one target DNA, wherein the primers are of different lengths, which allows for separation of the different primer extension products based on size using slab gel electrophoresis and autoradiography. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the method of Soderlund in view of Hoogendorn and Kuppaswamy could be improved to include analysis of polymorphic sites in multiple targets because Krook teaches the successful analysis of multiple polymorphic sites in more than one target DNA wherein the differences in length of primers for extension product reaction are indicative of the different targets. It would have been immediately apparent to the ordinary artisan that since the multiplexing method of Krook was also based on size differences between primer extension products, that the method of Soderlund in view of Hoogendorn and Kuppaswamy could be improved to include multiplexed primer extension product reactions, and that the difference in primer extension products could be further used to identify the polymorphic nucleotide present at each site. The ordinary artisan have been motivated to improve the method of Soderlund in view of Hoogendorn and Kuppaswamy using the multiplexing concept of Krook

for the obvious improvement of being able to analyze mutations in more than one gene or one region of a gene at a time. As applied to the rejection of claims 69-74 above, the ordinary artisan would have recognized that unlabeled dNTPs could be used as alternative to the labeled dNTPs taught by Krook for the obvious improvement of eliminating the use of harmful, radioactively labeled nucleotides.

Conclusion

9. No claims are allowable over the cited prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
5/27/03